II. REMARKS

Preliminary Remarks

A preliminary amendment was filed on May 8, 2001, requesting that the first paragraph of the specification be amended to identify parent applications 09/080,349 and 08/481,735. If the preliminary amendment was not received or cannot be entered, the applicants request that the Patent Office please so inform the undersigned.

The title and abstract of the application are amended so as to identify the elected invention, as requested in the official action.

In the specification, the paragraph beginning at page 6, line 15, is amended to state the current address of the ATCC, as requested in the official action.

Claims 2, 3, and 11 are canceled, claims 1, 4, 5, and 8-10 are amended, and new claims 12-20 are added.

Claim 1 is amended to be directed to a "method for inhibiting or preventing a T cell mediated autoimmune response associated with type I diabetes," support for which is found in the specification, for example, in the second paragraph on page 1, which describes type I diabetes as a disorder that is caused by an autoimmune response that results in destruction of insulin-producing pancreatic β cells; and in the paragraph bridging pages 3-4, which describes the effect of administering a gp39 antagonist as inhibiting or preventing a tissue-destroying T cell mediated autoimmune response associated with an autoimmune disorder such as type I diabetes. The body of claim 1 is amended to be directed to administering "a therapeutically or prophylactically effective amount of a gp39 antagonist selected from the group consisting of soluble CD40, CD40 fusion protein and an anti-gp39 antibody or a fragment thereof that binds gp39, support for which is found, for example, on page 4 (1st full paragraph). New claim 12 is directed to an anti-gp39 antibody or a gp39-binding fragment thereof comprising variable regions of monoclonal antibody 24-31 or 89-76, or of an antibody having the gp39 binding characteristics thereof. Anti-gp39 antibodies 24-31 and 89-76 are described on page 6 (middle of page). The use of gp39-binding fragments of anti-gp39 antibodies as gp39 antagonists as recited in new claims 12-16 is described on page 4, lines 12-17, and page 6, lines 8-14. Chimeric monoclonal anti-gp39 antibodies having constant regions and variable regions from different species are described on page 6. Gp39 binding characteristics of monoclonal antibodies 24-31 or monoclonal antibody 89-76 are

described in International Application Publication No. WO 95/06666 (see Example 3), the contents of which are incorporated into the present application (see p. 6).

Patentability Remarks

35 U.S.C. §112, First Paragraph

As amended, claim 1 identifies a disclosed group of anti-gp39 antagonists which operates to inhibit or prevent a T cell mediated autoimmune response associated with type I diabetes. The amendment of claim 1 is believed to obviate the rejections of the claims under 35 U.S.C. 112, 1st paragraph, stated on pages 3-5 (written description) and 6-7 (scope of enablement) of the official action.

35 U.S.C. §102(e)

Claims 1, 2, and 4-10 were rejected under 35 U.S.C. 102(e) as being anticipated by Noelle et al. (U.S. Patent No. 5,683,693; "the '693 patent"). The examiner points to columns 5-7 of the '693 patent as describing the present invention. As amended, the claims of the present application are directed to a method comprising administering a gp39 antagonist to inhibit or prevent a T cell mediated autoimmune response associated with type I diabetes. The '693 patent of Noelle et al. is entitled "Method for Inducing T Cell Unresponsiveness to a Tissue or Organ Graft with Anti CD-40 Ligand Antibody or Soluble CD40." As the title implies, the '693 patent describes administering a gp39 antagonist to induce tolerance to transplanted allogeneic or xenogeneic cells, but it does not describe administering a gp39 antagonist to inhibit or prevent a T cell mediated autoimmune response associated with type I diabetes. Withdrawal of the rejection is respectfully requested.

Claims 1, 2, and 4-10 were rejected under 35 U.S.C. 102(e) as being anticipated by Lederman et al. (U.S. Patent No. 5,993,816; "the '816 patent"). The examiner points to column 11 of the '816 patent as describing the present invention. The '816 patent is entitled "Methods to Inhibit Humoral Immune Responses, Immunoglobulin Production, and B cell Activation with 5C8-Specific Antibodies. Consistent with this title, the '816 patent relates to using a gp39 antagonist to inhibit B cell activation and humoral immune responses.

The destruction of islet beta cells in Type 1 diabetes is triggered and mediated primarily through T cell mediated cellular autoimmunity (Casares et al., Curr Mol. Med., 2001, 1(3):357-378; Campbell et al., J. Autoimmun, 1990, 3 Suppl 1:53-62, abstracts attached). The T cell mediated autoimmune responses that are prevented or inhibited by the present invention are expressly described in the specification as ones "involving cell-mediated immune mechanisms, as opposed to humoral immune mechanisms," (p. 3, bottom paragraph). The claimed method is expressly directed at inhibiting or preventing the T cell mediated cellular immune responses that cause the destruction of islet beta cells in Type 1 diabetes. Because Type 1 diabetes is initially triggered and primarily mediated through T cell mediated cellular autoimmunity, the claimed method operates to inhibit a T cell mediated cellular autoimmune response when no humoral response is present, and so is distinct from a method related to treating B cell activation and humoral immune responses associated with diabetes. The '816 patent does not describe or suggest administering a gp39 antagonist to inhibit or prevent a T cell mediated autoimmune response associated with type I diabetes. Withdrawal of the rejection is respectfully requested.

35 U.S.C. §102(a)

Claims 1, 2, and 4-10 were rejected under 35 U.S.C. 103(a) over the '693 patent of Noelle et al., alone or in combination with the '816 patent of Lederman et al., together with U.S. Patent No. 5,747,037 of Noelle et al., which discloses the 24-31 and 89-76 antibodies.

Applicants submit that neither the '693 patent of Noelle et al. nor the '816 patent of Lederman et al. describe or suggest the method for inhibiting or preventing T cell mediated cellular immune responses of the present claims. Accordingly, the claims are not rendered obvious by the disclosure of the 24-31 and 89-76 antibodies in U.S. Patent No. 5,747,037. Withdrawal of the rejection is respectfully requested.

Double Patenting

Claims 1, 2, and 4-10 were provisionally rejected for obviousness-type double-patenting over claims 13-26 of co-pending Application No. 09/223,634. Claims 13-17 in Application No. 09/223,634 are canceled, and remaining claims 18-26, listed in the

attachment, have been amended so that they are not directed to a method for treating diabetes. Withdrawal of the provisional rejection is respectfully requested.

Claims 1, 2, and 4-10 were rejected for obviousness-type double-patenting over claims 1-6 of U.S. Patent No. 6,328,964. Claims 1-6 of U.S. Patent No. 6,328,964 are directed to a method for preventing or inhibiting the symptoms of multiple sclerosis which, as stated in the restriction requirement in the present application, is a species of invention that is patentably distinct from the present invention. Withdrawal of the rejection is respectfully requested.

Conclusion

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If any points remain in issue, which the examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

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Attachment 1: Allowed claims 18-26 of U.S. Appl. No. 09/223,634:

U.S. Appl. : 09/223,634

Filed : December 31, 1998

Title : Methods of Treating Thyroiditis and Oophoritis With Gp39 Antagonists

Applicant : Randolph J. Noelle et al.

18. A method for treating oophoritis in a subject in need of such treatment comprising administering a therapeutically effective amount of a gp39 antagonist selected from the group consisting of soluble CD40, CD40 fusion protein and an anti-gp39 antibody or fragment thereof that binds gp39.

19. The method of claim 18 wherein said gp39 antagonist is an anti-gp39 antibody or fragment thereof that binds gp39.

20. The method of claim 19 wherein said antibody is a humanized antibody.

21. The method of claim 19 wherein said antibody is a chimeric antibody.

22. (Amended) A method for treating thyroiditis comprising administering a therapeutically effective amount of a gp39 antagonist selected from the group consisting of an anti-gp39 antibody or fragment thereof that binds gp39, soluble CD40 and a CD40 fusion protein.

23. The method of claim 22 wherein said gp39 antagonist is an anti-gp39 antibody or fragment thereof that binds gp39.

24. The method of claim 23 wherein said antibody is a humanized antibody.

25. The method of claim 23 wherein said antibody is a chimerized antibody.

26. The method of claim 22 wherein said gp39 antagonist is soluble CD40 or CD40 fusion protein.

Attachment 2: Abstracts of References Cited in Remarks:

1. Casares S, Brumeanu TD, Curr Mol Med 2001 Jul;1(3):357-78; Insights into the pathogenesis of type 1 diabetes: a hint for novel immunospecific therapies.

Type 1 diabetes is an organ-specific autoimmune disease whose incidence is increasing worldwide. At present, there is no effective therapy to prevent or cure this disease. The genetic background (MHC and non-MHC genes) and environmental factors (pathogens, drugs, and diet) are critical for the initiation of the autoimmune response against the pancreatic beta-cells. Recognition of the pancreatic autoantigens by T cells in a predetermined environment of antigen-presenting cells, costimulation, and cytokines is crucial for the selective activation of diabetogenic or protective/regulatory T cells. Once the autoimmune process is triggered, epitope spreading and sustaining the autoimmune responses by continuous antigen stimulation leads to expansion of effector cells, which launch the attack on the beta-cells. Despite of some controversy, most of the studies in humans and animal models suggest that CD4 (Th1) T cells are directly involved in the autoimmune attack by secretion of pro-inflammatory cytokines and recruitment of cytotoxic CD8 T cells. Secretion of anti-inflammatory cytokines by Th2 cells is protective against the disease. Therapy with peptides derived from major target antigens, such as glutamic acid decarboxylase 65 or proinsulin, can prevent the disease in animal models by rising protective Th2 cells. Herein, we review the recent progress in the immunopathogenesis of Type 1 diabetes and insights into the development of new diagnostic tools and antigen-specific immunomodulators, such as MHC-peptide chimeras.

PMID: 11899083 [PubMed - indexed for MEDLINE]

2. Campbell IL, Harrison LC., J Autoimmun 1990 Apr;3 Suppl 1:53-62; A new view of the beta cell as an antigen-presenting cell and immunogenic target.

Cellular autoimmunity is thought to be primarily responsible for the selective destruction of islet beta cells in Type I diabetes. Why the T lymphocyte reacts to self and recognizes the beta cell as foreign, as against the other endocrine islet cells, is unknown. One key issue is whether the beta cell itself is capable of presenting autoantigen(s) and thereby breaking T lymphocyte tolerance. In this paper we discuss current concepts of antigen presentation and relate these to recent findings from our laboratory, suggesting that the beta cell can be induced to display many of the phenotypic properties of classical antigen-presenting cells, including induction of MHC and ICAM-1 expression and production of IL-6. Finally, a model is presented which provides a new view of the initiation and perpetuation of autoimmune beta-cell destruction in Type I diabetes.

PMID: 1971174 [PubMed - indexed for MEDLINE]